

## NTSAD Position Statement 2019 Update

### “Standards for Tay-Sachs Carrier Screening”

#### **Background:**

Tay-Sachs disease (GM2 gangliosidosis, type 1) is an autosomal recessive neurodegenerative disease caused by deficient activity of the enzyme hexosaminidase A (Hex A) due to biallelic pathogenic variants (mutations) in the *HEXA* gene. The frequency of carriers for Tay-Sachs disease in the general population is approximately 1 in 300. In persons of Ashkenazi Jewish or French-Canadian background, the carrier frequency is much higher, at about 1 in 30. The carrier frequency is also increased in several other populations, including individuals of Cajun background.

Standard preconception and prenatal care for individuals of these select backgrounds includes offering carrier screening for Tay-Sachs disease and other autosomal recessively inherited diseases relevant to one's genetic background. If both parents are found to be carriers of the same condition prior to conception, the couple can be offered genetic counseling to discuss reproductive options (including sperm or egg donation from a non-carrier, using an unaffected donor embryo, or *in vitro* fertilization with preimplantation genetic testing) and adoption to maximize their chances of having unaffected offspring. If screening is performed after conception, at-risk couples can be offered genetic counseling to discuss prenatal diagnosis (chorionic villus sampling or amniocentesis) to determine whether the fetus is affected with Tay-Sachs disease.

#### **Enzyme Activity Analysis versus DNA Screening Tests:**

Tay-Sachs disease carrier screening programs were initially developed in the 1970s to address the high prevalence of Tay-Sachs disease in the Ashkenazi Jewish population. Large scale carrier screening has been performed by measuring Hex A enzyme activity in serum or leukocytes via a blood sample. This technique allows for inexpensive, highly sensitive and reliable carrier screening for large numbers of individuals who desire screening for Tay-Sachs disease. The utilization of Tay-Sachs carrier screening has been impactful and regarded by many as a model public health genetic screening initiative. In the 1970s, there were approximately 60 Ashkenazi Jewish children born per year with Tay-Sachs disease in the U.S and Canada, and approximately 20 years later, this number had decreased to 3-5 affected children per year (Kaback, et al., 1993).

While Hex A enzyme activity testing has excellent diagnostic sensitivity, there are associated limitations when used for carrier screening, including false positive results related to the presence of pseudodeficiency alleles (gene variants that affect the assay result, but not *in vivo* enzyme function) as well as indeterminate (i.e., inconclusive) results. Other limitations include issues related to temperature stability of blood specimens, the use of oral contraceptive medication, the need for testing Hex A enzyme activity in leukocytes of females who are pregnant due to the high frequency of inconclusive results from serum, and an inability to detect rare B1 pathogenic variants of the *HEXA* gene (variants that may show *in vitro* enzyme activity in the non-carrier range but which are, nonetheless, deleterious). Positive Hex A results (i.e. low Hex A enzyme activity) in carrier couples

requires follow-up molecular testing to define the underlying pathogenic variant(s) prior to prenatal molecular diagnosis or pre-implantation genetic testing.

DNA-based screening for Tay-Sachs disease became available in the 1990s using genotyping, a molecular technology that detects a limited number of pre-specified pathogenic variants within a gene. In persons of solely Ashkenazi Jewish genetic background, genotyping for three founder pathogenic variants in the *HEXA* gene has 92-98% diagnostic sensitivity in identifying carriers (Bach et al., 2001). This same genotyping in people who are not of Ashkenazi Jewish background detects only about 20% of Tay-Sachs carriers (Triggs-Raine et al, 1990); use of a six pathogenic variant panel for non-Jews detects about 60% of carriers (Kaback, et al, 1993).

According to data from the Pew Research Center, American Jewish intermarriage rates have risen from 17% to 58% in the past four decades (Pew Research Center, 2013). Therefore, persons self-identifying as “Ashkenazi Jews” who are currently of reproductive age are less likely to be of solely Ashkenazi Jewish background than previous generations of those who identified as such. As Ashkenazi Jews become less genetically homogeneous, DNA screening via genotyping for a select number of pathogenic variants has increasingly reduced diagnostic sensitivity for this group, raising concern for continued use of this method to screen Ashkenazi Jews in America.

In the last decade, full-exon gene sequencing via Next Generation Sequencing (NGS) has emerged as an efficient, cost-effective and sensitive method for detecting pathogenic variants throughout a given gene, in contrast to genotyping which only detects a limited set of pre-determined pathogenic variants. NGS is currently used as a tool for broad reproductive carrier screening, including *HEXA*. Screening via NGS of the *HEXA* gene has several advantages over Hex A enzyme activity testing: NGS testing can be performed on diverse sample types including blood and saliva, it is less likely to be affected by sample temperature or transport conditions, it is not affected by pregnancy status or medication use, and B1 and pseudodeficiency alleles can be identified and appropriately interpreted. Limitations of NGS include the inability to detect non-coding pathogenic variants and to properly classify some variants of uncertain significance (VUS) (i.e., sequence variants whose biologic significance has not yet been determined). As most molecular diagnostic laboratories performing carrier screening do not report out VUS, it is possible that a VUS may be pathogenic and not reported as such. The continuous updating of variant databases is critical to ensure the most accurate classifications of previously unclassified variants in the *HEXA* gene. Of note, two recent studies suggest equal or better performance characteristics of full exon sequencing by NGS of the *HEXA* gene compared to Hex A enzyme activity testing for Tay-Sachs carrier screening (Hoffman et al, 2013; Cecchi et al, 2019).

### **Summary Points Regarding Carrier Screening:**

- Full-exon gene sequencing via NGS is a highly sensitive molecular test that detects coding sequence changes throughout the *HEXA* gene for Tay-Sachs disease and has a high carrier detection rate across all ethnic groups. In rare cases, this technology

is limited by the inability to detect some non-coding pathogenic variants or to properly classify some VUS.

- Genotyping is a molecular test that detects the presence of a select number of pre-specified pathogenic variants within the *HEXA* gene. It is less sensitive than full-exon gene sequencing by NGS, and in most instances, should not be the test of choice when screening for carrier status for TSD.
- Tay-Sachs disease carrier screening via Hex A enzyme activity testing is a sensitive assay for carrier detection. Of note, subsequent molecular testing may be needed to allow for utilization of reproductive options for carrier couples, and leukocyte testing (rather than serum testing) should be ordered for Tay-Sachs disease carrier screening in women who are pregnant or using oral contraceptive medication.
- Current data supports a shift toward the routine use of full-exon *HEXA* NGS for Tay-Sachs carrier screening in individuals of all ethnic backgrounds due to the benefits and few limitations of NGS, while continuing to regard Hex A enzyme activity testing as another reliable method for Tay-Sachs carrier status detection.

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